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Stress, immunity, and the management of calves[1]

Lindsey E. Hulbert[2] and Sonia J. Moisá
Department of Animal Sciences and Industry, Kansas State University, Manhattan 66506

ABSTRACT

Despite many advances in management and housing of dairy calves, 1 in 10 US dairy heifers die before weaning. A better understanding of the internal and external stimuli that contribute to the physiological and behavioral responses of calves to stressors is needed to reduce the risk of morbidity and mortality. Feeding calves their first meal is crucial, as successful passive transfer reduces the risk of mortality and morbidity. Sexually dimorphic immune and stress responses appear to be present in young cattle, but more research is needed to determine if this is caused by human bias for female calves. After that first feeding, 1 in 10 heifers and most bull calves in the United States are transported to specialized calf-raising facilities, yet information is lacking on the newborn calf stress response during transit. Whether calves are raised on site or at a calf ranch, individual housing systems are commonly used in the United States to reduce the risk of pathogen exposure and provide individual feeding and healthcare. However, health, growth, and social implications may be present for calves in alternative systems with greater space allowance than conventional systems or group housing. Disbudding and castration are typically performed at an early age for dairy calves during the pre-wean stage. These stressors often take place when the calf has decreased passive transfer of Ig and immunity is developing. Availability of pain mitigation through anesthetics and analgesics is limited, but evidence indicates that analgesics attenuate suppressed leukocyte function during these procedures. Solid-feed intake is a primary measure for determining weaning readiness, but some milk replacer formulas may influence the calf's oral behaviors before weaning; therefore, alternate weaning methods may need to coincide with alternate milk replacer formulas. The calf's behavioral and stress response at weaning may influence its immunity during the transition from individual to group housing (commingling). Alternate commingling strategies and nutritional supplements may help with this transition, but more research is needed to explore feasible alternatives. Optimizing the calf's health and well-being at these early stages may improve its long-term health and welfare.
Key words: early life, immunity, stress, neonate

INTRODUCTION

Welfare of dairy calves can be improved through management strategies that help improve resilience to stress and disease. Scholars and producers often debate if performance is a measure of animal welfare (Moberg and Mench, 2000; Rollin, 2003; Fraser, 2008; Appleby et al., 2011). Among mature animals, performance is defined and measured, and some clear implications for animal welfare were found (Grandin, 2015). For example, age at calving, milk production, quantity and quality of semen, and quality and quantity of meat at slaughter are performance measures for dairy heifers, cows, bulls, and steers. For these mature animals, the links between performance and animal welfare are established and understood. A cow may not let down milk if she is mishandled (Seabrook, 1980; Rushen et al., 1999). A heifer may have low conception rates if she has low or high BCS (Davis Rincker et al., 2011). A bull may produce less quantity and quality of semen if he is chronically sick (Smith Thomas, 2014), and a steer may produce lactate that ruins meat quality if he is mishandled during slaughter (Gruber et al., 2010). But, what is performance for the dairy calf and are there clear connections to their short-term and long-term welfare?

Performance measures may not always be appropriate well-being indicators during certain critical windows for dairy calves. For example, a benchmark of calves to double their birth weight by weaning was cited as

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[2]Corresponding author: lhulbert@ksu.edu

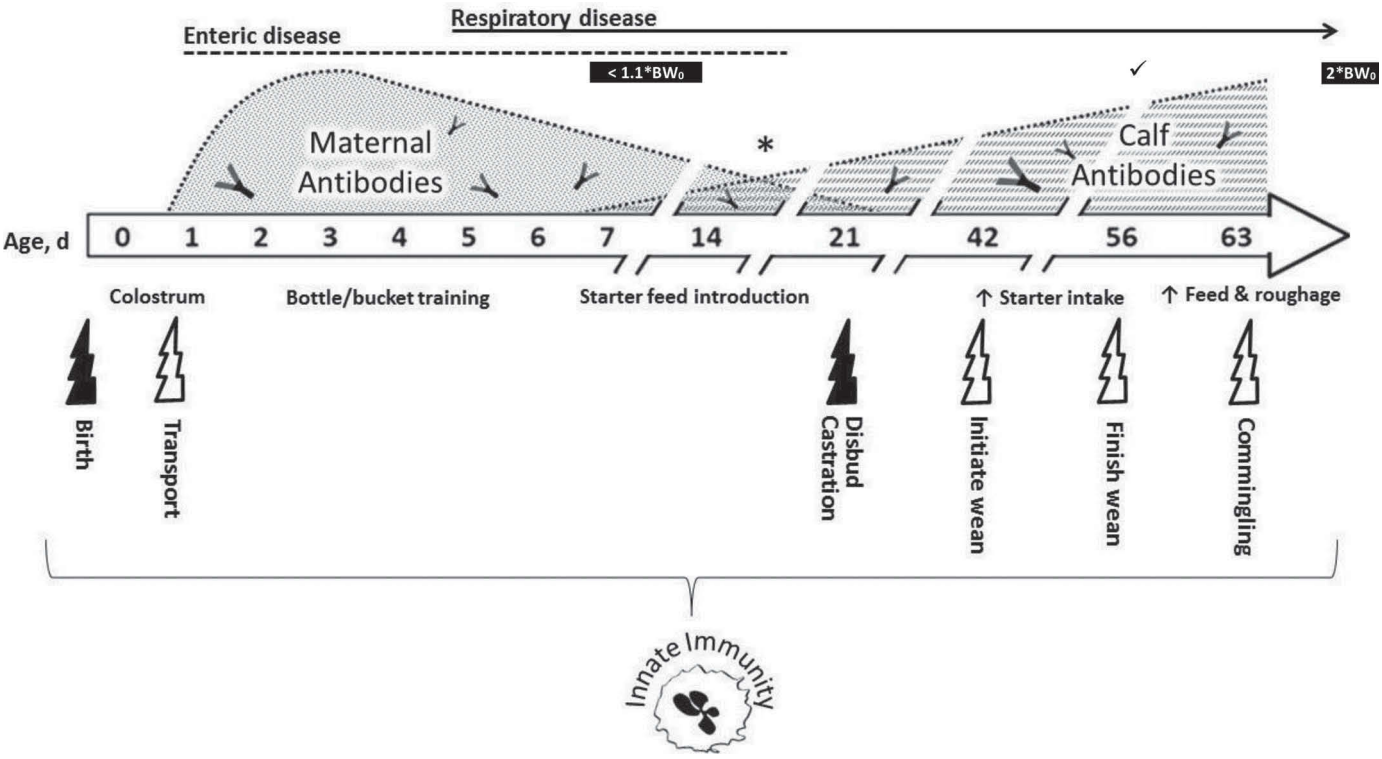

Figure 1. Dairy calf stress, immunity, and management timeline. Potential inflammatory (black-bolt) and psychological (white-bolt) stressors are inevitable for the developing, hand-fed dairy calf. Birth is the first direct stressor in a calf's life, although the prenatal environment can influence the fetal stress-axis. Calves must be provided colostrum to gain passive transfer of maternal antibodies (Y). Calves that experience difficult births are more likely to have failure of passive transfer (FPT); bull-calves also have a higher rate of FPT than heifers, regardless of birthing difficulty. Transportation is a known stressor to mature animals. One out of 10 heifers and most bull calves are transported to a calf-raising facility within a day after birth. The stress of birth and transportation may influence bottle training of calves; over one-half of US dairy heifers were fed medicated milk replacer. High quality feed (starter) was introduced to healthy calves at an average of 1 wk of age and water at an average of 2 wk of age. Roughage is not introduced until enteric disease risk decreases, which is after 3 wk of age. One out of 3 heifers experience enteric disease (dashed-line) in the preweaning stage; therefore, 7 out of 10 calves are penned individually to avoid disease transmission. Typically, producers choose to castrate male calves and disbud between 3 and 4 wk of age, which is an inflammatory stressor. This is the same period (*) when antibodies from passive transfer are low, and the calf is just beginning to have its own antibody responses to environmental microbiota. The average age calves are weaned from milk or milk replacer is 8.2 wk, but weaning is often initiated 1 to 2 wk before by withdrawing a significant portion of the liquid diet, thus stimulating calves to consume more starter. Calves typically are not fully weaned until the last portion of liquid diet is removed. After weaning, calves that were individually housed will be moved into groups (commingling), which may be another potential psychological stressor that can exacerbate respiratory disease, which is the most common cause of morbidity and mortality in postweaned calves. A benchmark (checkmark) was proposed for calves to double birth weight by weaning, but on average, US heifers double birth weight about 2 wk after weaning ($2*BW_0$). Preweaning weight gain is marginal ($<1.1*BW_0$) in the first week or 2 of life.

a best standard practice for calf raisers (James, 2008; AJCA, 2015). However, the majority of US dairy calves wean at an average of 8.2 wk of age (Figure 1), which is 6 to 10 mo earlier than if dams weaned calves naturally (Jones and Heinrichs, 2007). If one considers the many management and critical windows in the pre-weaned calf's timeline (Figure 1), it is not surprising that the majority of US heifers do not double their birth weight until at least 2 wk after the average weaning age (Figure 1; NAHMS, 2007). Furthermore, most calves have little weight gain after the first week of life (Figure 1; NAHMS, 2007). This is not uncommon for many neonates; in pediatric medicine, healthy human infants are expected to lose some weight after birth; then they should at least reach their birth weight at their 2-wk checkup (Tawia and McGuire, 2014).

Milk and milk replacer are valuable commodities. Therefore, it is more economical in the short term to optimize the amount and time that milk products are fed to dairy calves (Davis and Drackley, 1998). Weaning dairy calves from liquid milk or milk replacer is likely a different type and severity of stressor than weaning beef calves from their dams (Hulbert et al., 2011a,c). Some researchers suggested increasing milk replacer nutritional content to attain high pre-wean ADG (high plane of nutrition, **HPN**; Raeth-Knight et al., 2009; Davis Rincker et al., 2011; Soberon et al., 2012). However, many research experiments have not

replicated such a benchmark through accelerated milk nutrition alone (Jones and Heinrichs, 2007; Hill et al., 2010, 2011b, 2013). Regardless if HPN calves reach this benchmark before weaning, the weaning timeline may need to be altered for HPN calves. For example, conventionally fed calves were more motivated to eat solid feed (calf starter) than HPN-fed calves before weaning, which helped them with the transition from liquids to full solids during step-down weaning (Figure 1; Ballou et al., 2015; Hulbert et al., 2015). The HPN calves appeared more frustrated during weaning; they did not consume as much starter after the first bottle was removed (Figure 1) and they increased their nonnutritive oral behaviors. Dry matter intake at weaning was highly correlated with improved 305-d ME milk, fat, and protein production in a prospective study of 795 Holstein calves from 21 commercial dairies (Heinrichs and Heinrichs, 2011). In another meta-analysis, a calf's motivation to feed was a better predictor of health and performance than its colostrum passive transfer status (Bateman et al., 2012). This motivation to consume solid foods at an early age may influence HPN-calves' immune systems because they had less ex vivo innate immune responses before weaning, but after weaning, ex vivo immune measures did not differ from conventionally fed calves (Nonnecke et al., 2003; Foote et al., 2005, 2007; Ballou, 2012; Obeidat et al., 2013; Ballou et al., 2015). Once HPN calves were no longer on a milk replacer diet, they also showed less signs of clinical sickness, faster inflammatory responses, and speedier recovery than conventionally fed calves when challenged with aerosolized *Mannheimia haemolytica* or oral *Salmonella enterica* serotype Typhimurium (Ballou et al., 2015; Sharon et al., 2015). Nonetheless, environmental influences and management strategies on immune development are multifaceted; if just one component of the calf's management timeline is altered, the other factors and critical windows need to be considered.

Although some of the pre-weaning strategies for dairy calves are artificial critical windows, the first day of life is a biological critical window. Calf raisers and researchers have long recognized that a normal birth coinciding with immediate access to high-quality colostrum decreases the risk of mortality and morbidity (Tyler et al., 1999; McGuirk and Collins, 2004). The second postnatal critical window appears to fall within the first week or 2 after birth; at this stage, calves are extremely susceptible to enteric disease. Recent reports from NAHMS reveal that 1 out of 3 dairy calves experience enteric disease (Figure 1; NAHMS, 2007). Neonatal calves have developing digestive tracts and inadequate thermoregulation, which may be major contributors to the lack of weight gain during the first 2 wk of life (Tao and Dahl, 2013). Furthermore, disease prevalence and the knowledge that calves are born without maternal antibodies may have led to the misconception that calves are born without an immune system. Calves are indeed born with immunity; calves retain the same amount peripheral leukocytes responsible for cellular innate immunity from birth through maturity (Figure 1; Kampen et al., 2004). Rather than lacking immunity, neonatal calves lack immunocompetence. A closer look at the hours and weeks following birth may allow producers to make management decisions that help calves develop immunocompetence sooner.

A resilient stress response coupled with immunocompetence rapidly develops during the critical windows around calving (Morel et al., 2015). The average dairy calf faces many potential stressors in the pre-weaning period, including birth, transportation, disbudding/castration, weaning, and commingling (Figure 1). Most of these stressors appear inevitable in calf raising production systems, but they are manageable if the calf timeline is considered (Figure 1). Although the pre-weaning stage accounts for only a 4% of the heifer's life and 10% of a dairy-beef calf, development of the calf's stress and immune systems may affect performance and overall well-being for an animal's entire life; therefore, this manuscript will review how the hypothalamopituitary adrenal (**HPA**) axis and immune system develop together to make the calf immunocompetent (Figure 2) and resilient. A better understanding of the immune-HPA axis will help evaluate the most common US conventional calf management strategies.

IMMUNE-HPA AXIS

Immunocompetence is defined as the ability to defend oneself against potentially damaging microbes and parasites (Matthews, 2002; Blalock and Smith, 2007; Dantzer et al., 2008; Fleshner, 2013). Several systems are involved with immunocompetence, which include barriers, surveillance, combat, control, and documentation. Barriers include the skin and mucosal barriers (e.g., respiratory tract and digestive system). These barriers are formed with commensal microbiota. The surveillance-and-combat wing of the immune system includes residential leukocytes such as phagocytic and granulocytic cells (e.g., macrophages, neutrophils, eosinophils, and basophils), which are considered innate because the calf is born with these cells and humoral compliment factors, and they are fully functional before having any exposure to microbial-associated molecular patterns (**MAMP**) from bacterium (Figure 2; Kampen et al., 2006).

For example, calves are born with neutrophils that circulate in the blood and survey for MAMP and other signals; they are short-lived and are replaced every 24

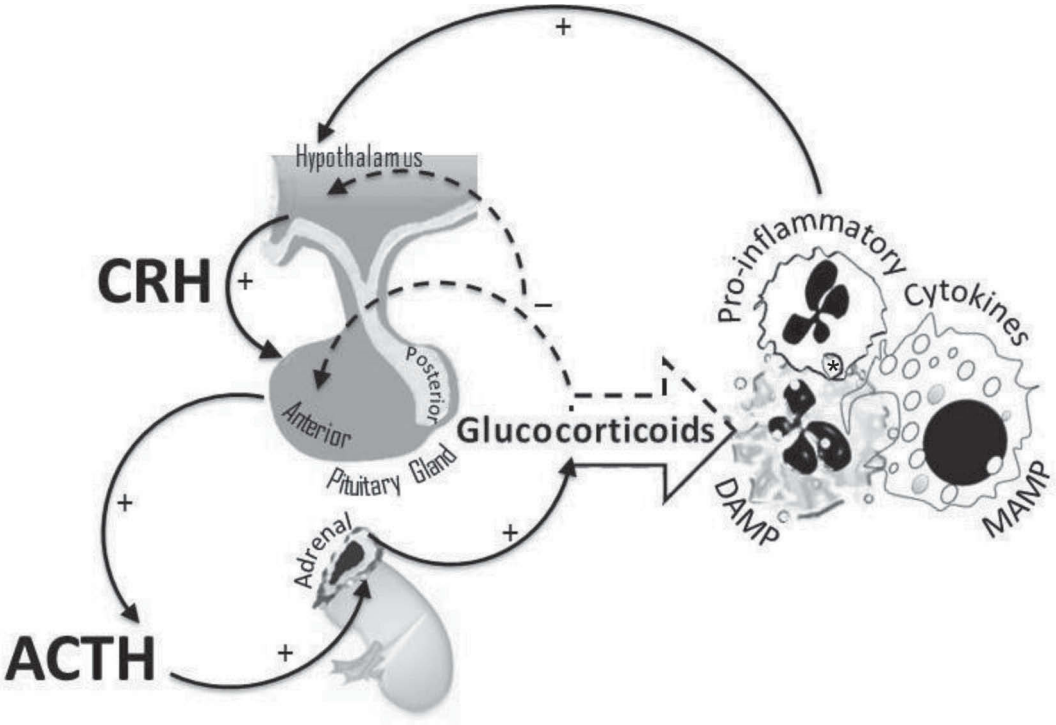

Figure 2. The hypothalamopituitary adrenal and inflammatory axis (HPA-immune axis) can be activated (solid-arrowed line) by inflammatory markers such as apoptotic and necrotic cells, prostaglandins, pro-inflammatory cytokines, danger-associated molecular patterns (DAMP), and molecular-associated molecular patterns (MAMP). Upon activation, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the corticotrophs in the anterior pituitary to secrete ACTH. The main targets of ACTH are the cortexes of the adrenals, which cause glucocorticoid (GC) secretion. Glucocorticoids provide a negative feedback (dashed-circled line) signal to the hypothalamus and anterior pituitary, and GC directly provide both pro- and anti-inflammatory signals to immune tissues. Shown are diagrams of neutrophil phagocytosing a bacterium (*), and a MAMP-activated macrophage phagocytosing a necrotic, DAMP-producing neutrophil.

h in healthy cattle (Paape et al., 2003; Hulbert et al., 2011a). When neutrophils receive signals (e.g., LPS from cell wall of gram-negative bacteria) to leave circulation, they then undergo diapedesis (adhesion) and migrate to the site of infection to phagocytose (engulf) bacterium. Intracellular enzymes and free-radicals (oxidative burst) are released to kill the bacterium. These damaging molecules are both deadly for the bacterium and the neutrophil (danger-associated molecular patterns, **DAMP**; Figure 2). Therefore, apoptosis, proper cellular death of neutrophils, can be activated to prevent exposure of DAMP to surrounding tissues or into the circulation and lymphatics. Depending on the severity of infection, not all neutrophils undergo apoptosis, some become necrotic, and DAMP are released (Chang et al., 2004; Buckham Sporer et al., 2007). Similar to lymphocytes, macrophages, such as T cells, can be differentiated into subtypes depending on the local milieu of signals. When both MAMP and DAMP are produced in a severe inflammatory state, macrophages may become pro-inflammatory, but signals from cells undergoing apoptosis may stimulate macrophages to differentiate into quiescent phagocytic cells (e.g., kupffer cells of liver, osteoclasts in bone, microglia in brain) and minimize the amount of cellular debris, preventing inflammation, or macrophages can secrete anti-inflammatory cytokines to regulate a systemic response (Murray and Wynn, 2011). Whether severe tissue damage occurs under sterile or unsanitary conditions the HPA axis is influenced by the immune system (Boutzios and Kaltsas, 2000). Likewise, the HPA axis modulates the immune system (Mitra et al., 2009).

In mature animals, the adaptive immune system includes specific antibodies to document pathogens. Antibodies help control the innate immune response by minimizing the amount of proinflammatory cellular responses (Bateman et al., 1989; Bayne, 2003). Young animals without a developed adaptive immune system rely on the HPA axis which serves as the primary regulator and modulator of immunity. The classic HPA response is depicted in Figure 2. When a mature animal perceives stress, the HPA axis is activated, and stress hormones, most notably glucocorticoids (**GC**), are released to provide homeostatic feedback (Figure 2; Millington, 2007). Several factors within the immune system directly and indirectly activate the

HPA axis (e.g., cytokines, DAMP, MAMP; Matthews, 2002; Blalock and Smith, 2007; Dantzer et al., 2008; Fleshner, 2013). Glucocorticoids provide an important regulatory role in a stress or immune response (Figure 2). For example, peripheral administration of LPS (i.e., MAMP from the cell-wall of gram-negative bacteria) models a septicemic-like response, marked by decreased leukocytes and increased, prolonged secretion of GC (Burdick et al., 2012; Carroll et al., 2015). The GC help inhibit the damage that a septicemic challenge can cause. As calves age, increased GC were observed, in conjunction with increased mononuclear cell function, but percent neutrophils circulating remained the same in most calves (Hulbert et al., 2011a). However, calves that ate more starter after early weaning was initiated had reduced circulating neutrophils. Calves that did not respond to early step-down weaning with increased feed intake had reduced monocyte function. This is an indicator that solid feed intake is a coping strategy for calves (Hulbert et al., 2011a).

Another common misconception is that all stressors are bad for animals. Acute stressors may actually improve immunocompetence and resilience (Moberg and Mench, 2000; Mitra et al., 2009). Moderate stressors such as handling caused low concentrations of corticotropin-releasing hormone in mice to be released, but concentrations were not elevated enough to cause ACTH release. Rather, handling stress caused the anterior pituitary to increase sensitivity to pro-inflammatory cytokines through increased expression of IL-1 receptors (Blalock and Smith, 2007). Therefore, low concentrations of IL-1 produced during an infection directly stimulated the pituitary gland to produce ACTH and subsequently, GC. Stress-associated neutrophilia is influenced by changes in migration and adhesion molecules such as L-selectin and β2-integrin (Weber et al., 2001; Diez-Fraile et al., 2003, 2004). Multi-factor stressors, such as transportation combined with handling, caused neutrophil downregulation of L-selectin and a greater percentage of circulating neutrophils (Buckham Sporer et al., 2007; Hulbert et al., 2011a,c). Researchers speculated that this mechanism helps prevent too many neutrophils from leaving the periphery and causing an overabundance of inflammation and damage to host tissue (Buckham Sporer et al., 2007). Overactive neutrophils may cause damage to lung tissue after exposure to *Mannheimia haemolytica*, the primary pathogen associated with bovine respiratory disease or shipping fever (Buckham Sporer et al., 2007; Duff and Galyean, 2007). Likewise, in healthy cattle, immune stimulation can be observed after stressors.

Calves that are resilient and immunocompetent should have a well-regulated HPA-activity, physiological function, and coping behaviors in the presence of multiple stressors. A well-functioning HPA axis includes an established circadian GC cycle (Chung et al., 2011) and low concentrations of GC before an acute stressor. Following an acute stressor, a responsive HPA axis displays a short duration but high intensity of circulating GC (Alkadhi, 2013).

The Birth Critical Window

Calf raisers can help calves build immunocompetence and resilience before birth. For over 5 decades, researchers have found that offspring from stressed dams have permanent alterations in their resilience to stressors and immunocompetence (Matthews, 2002; Veru et al., 2014). Depending on the severity and duration of stressors in utero, the weaned calf may end up with increased peaks of ACTH and reduced GC clearance during routine stressors, such as weaning and disbudding (Lay et al., 1997). Although maternal neuroendocrine responses may not directly affect the fetus, the hormones released from maternal stress directly alter placental function (Collier et al., 2002). Severe maternal stress can induce hypoxia and acidosis in the fetus as increased maternal catecholamines cause changes in placental blood vessels and tight junctions (Matthews, 2002).

The days before parturition are noted by a change in HPA function, even among fetuses of low-stressed dams. Among many species (mice, pigs, rats, sheep), the negative feedback provided by GC is inhibited (Figure 2) and fetal circulating GC steadily increase in circulation. Contrary to the common association with stress and increased circulating GC, calves that experienced dystocia had low levels of GC in circulation rather than elevated GC (Table 1; Matthews, 2002; Murray and Leslie, 2013). The maturation roles caused by increased fetal GC are varied (including liver function, energy homeostasis), but most notable are the direct stimulation of tight junction and mucosal formation in the digestive and respiratory tracts (Liggins, 1994; Gluckman et al., 1999; Bayne, 2003; Teitelbaum and Allan Walker, 2005). Ingested colostrum just after birth also helps mucosal barriers form, thus providing nutrients and scaffolding to help microbes make the calf their host. These factors are key in preventing pathogen invasion without eliciting an inflammatory response. From the moment the calf is exposed to the vaginal canal, microbiota start inhabiting the calf's skin, respiratory system, and digestive system (Stilling et al., 2014). These mucosal barriers and the microbiota that develop on them may be the key factors for preventing enteric and respiratory diseases (Figure 1).

The birthing process alone can be stressful for the calf (Murray and Leslie, 2013), and not all calves cope well with the stress and inflammation associated with

Table 1. The acute and long-term effects of potential stressors of typical dairy heifer and bull calves

		Immunocompetence or resilience outcome		
Event	Stressor	Acute effects	Long-term effects	References
Birth	Normal	↑ Successful passive transfer of maternal Ab[1]	↓ Risk of disease	Tyler et al., 1999
	Dystocia	↓ Calf vitality; ↓ passive immunity transfer; ↓ GC[2]; ↑ glucose	↑ Risk of morbidity and respiratory disease; ↓ weight gain	Lombard et al., 2007; Civelek et al., 2008; Barrier et al., 2013; Murray et al., 2015
Transport	Transportation	↑Mobilization of energy and protein metabolism; ↑circulating neutrophils with more adhesion expression	↓ GC and Epi[3] responses to sickness	Hulbert et al., 2011b; Burdick et al., 2010, 2011; Ishizaki and Kariya, 2010
Housing	Individual	↓ Risk of enteric disease transmission	↑ Basal GC	NAHMS, 2007
	Group	↑ Respiratory disease; ↑ starter intake	↓ Stress at weaning but ↑ stress response to handling and transport stress; ↓ cleanliness	Cobb et al., 2014a; Abdelfattah et al., 2015
	Increased space	↑ GC clearance after ACTH challenge	↓ Basal GC; ↑ cleanliness; ↑ADG	Gupta et al., 2007; Laber et al., 2008; Calvo, 2012
Castration	Surgical	↑ Inflammatory leukocyte responses	↓ ADG	Fisher et al., 1997; Earley and Crowe, 2002; Ting et al., 2003; Sutherland et al., 2013; Ballou et al., 2013
	Nonsurgical	↓ Risk of pathogen exposure	↓ ADG	Earley and Crowe, 2002; Bretschneider, 2005; Pang et al., 2009
Disbudding	Iron	↑ Inflammatory response	↑ Risk of pathogen exposure from pulled scabs	Sylvester et al., 1998
	Paste	↑ Behavioral signs of discomfort	↓ Risk of pathogen exposure	Molaei et al., 2015
Weaning	Early age	↓ Neutrophil responses; ↑ latency of starter[4]	↑ First-lactation milk yield	Hulbert et al., 2011a; O'Loughlin et al., 2011; Soberon et al., 2012
	Abrupt	↓ Neutrophil responses; ↑ leukocytes and lymphocytes; ↑ vocalization	↑ Growth performance	Haley et al., 2005; Lynch et al., 2010; Hulbert et al., 2011c; Lambertz et al., 2015
	Stepdown	↑ Cortisol; ↑ neutrophil L-selectin	↓ Glutathione reductase	Burke et al., 2009; Hulbert et al., 2011c
Commingling	Before weaning	↑ Starter intake[5]; ↑ cross-sucking	↑ Growth; ↓ respiratory incidences; ↑ milk stealing	Jensen, 2003; Bach et al., 2010
	After weaning	↓ Cortisol and L-selectin and ↑ neutrophil activity	↑ ADG	Hulbert and Ballou, 2012; Cobb et al., 2014b

[1]Antibodies.

[2]Glucocorticoids.

[3]Epinephrine.

[4]Amount of days for calves to consume enough starter so second bottle could be removed in stepdown weaning.

[5]Calves meet starter intake requirements so weaning is less gradual.

birth. In 2006, US dairy producers reported that 6% of calves died at birth and 2% did not survive the first 48 h after birth (NAHMS, 2007). Most of these deaths are attributed to dystocia (Lombard et al., 2007), but calves that survive dystocia carry higher risk of morbidity and mortality during the pre-weaning stage (Lombard et al., 2007). Tissue damage caused from a difficult birth, even without any microbial exposure, may illicit an inflammatory response from increased DAMP (Figure 2; Stilling et al., 2014). The HPA axis may be underdeveloped at birth; therefore, the inflammatory response may not be well controlled. These factors may contribute to a low-vitality calf because an under-regulated inflammatory response only exacerbates the underdeveloped thermoregulation system, and worsens hypoxia from a difficult birth (Murray and Leslie, 2013). Calf vitality assessment may key management practice to improve the calf's first direct experience with stress—the stress of birth. Murray and Leslie (2013) provide an overview of the importance of calf vitality measures and some therapies that may be needed to help calves that experienced a difficult birth.

The Colostrum Critical Window

Calves that can be identified for low vitality also are less motivated to stand up and suckle (Campler et al., 2015). These precocious behaviors (standing, exploring, suckling) are indicators that calves will have greater success at obtaining their first meal (Ventorp and Michanek, 1991; Godden, 2008; Murray and Leslie, 2013). The first meal for bovine species must obtain an adequate amount of colostrum within the first 24 h critical window (Godden, 2008). Calves that not received colostrum are 74 times more likely to die in the first 3 wk of life (Wells et al., 1996). Failure of passive transfer (**FPT**) of maternal antibodies accounted for almost 40% of the deaths in an experiment with 3,479 calves (Tyler et al., 1999). Despite the fact that almost 9 out of 10 dairy producers reported hand-feeding colostrum, 1 out of 10 heifers died (NAHMS, 2007).

Although the presence of the dam helps with Ig absorption from colostrum (Quigley et al., 1995), calves that were allowed to suckle from the dam ingested inadequate volumes of colostrum and increased their risk of colostrum-borne pathogens (Ventorp and Michanek, 1991; Rajala and Castren, 1995; Svensson et al., 2003). Over 60% of heifers are hand-fed colostrum via bottle, whereas one-third of calves were fed colostrum by esophageal feeder (Shivley et al., 2015). If low vitality calves are identified, perhaps more than gavage is needed to decrease their risk of death. Low-vitality calves may need analgesics and more care with thermoregulation to improve Ig absorption from colostrum because the inflammatory response and hypoxia may inhibit passive transfer even if colostrum quantity and quality is constant (Murray and Leslie, 2013). Calves with low vitality have an underdeveloped suckling response on d 1 of age (Murray and Leslie, 2013). In human medicine, gavaged infants were encouraged to perform nonnutritive sucking, which in turn increased their feeding success rate compared with gavaged infants who were not encouraged to suckle (Bernbaum et al., 1983). The first few days of life serve as a crucial critical window for training the calf to suckle from a bottle or bucket, and the colostrum feeding may contribute to the success rate of training.

Maternal antibodies from colostrum appear to stay in the calf's system for the first 3 wk of life (Figure 1). However, the calf's cellular or humoral immune systems at 3 wk of age do not appear to be vastly different from wk 1 (Kampen et al., 2006). Through increased exposure to novel microbes, the calf starts to develop its own antibodies after about 3 wk (Figure 1). Vaccination type and timing may need to be considered in lieu of maternal antibodies. Calves with successful passive transfer vaccinated at 2 wk against bovine viral diarrhea type 1 had a more severe systemic inflammatory response to aerosolized bovine viral diarrhea at 10 wk of age than calves provided the vaccine at a later age (Ellis et al., 2001). One solution may be to use intranasal vaccination because research suggests this medium interferes less with maternal antibody production (Gorden and Plummer, 2010; Niewiesk, 2014).

Colostrum for Male Dairy Calves

The morbidity and mortality rates for pre-weaned dairy bull calves are not reported in literature, but rates were expected to be greater than heifers because they are at high risk for FPT. Bull calves from dairy production were long considered to be a by-product or even a waste product of dairy production, and their postnatal care did not appear to be a priority (Lovell and Hill, 1940). In recent years, the value of 1-d-old Holstein bull calves tripled because more dairy calves were sold for beef due to an annual decline in beef cattle (Burciaga-Robles, 2015). Almost 1 in 5 steaks consumed in the United States were from a dairy breed in 2012 (Wardynski, 2012). Dairy-beef calves were raised and managed very similar to dairy heifers until about 100 to 120 d of age, at which time most enter commercial feedlots (Zinn, 2015). At the feedlot, Holstein beef calves had a greater risk for diseases such as liver abscesses compared with beef calves, which may be contributing to slower weight gain at the feedlots (Nagaraja and Chengappa, 1998). Some evidence is available that the immunocompetence (or lack thereof) of male calves may be intrinsic.

Among purebred, dam-raised Brahman calves, males appeared to be less resilient to corticotropin-releasing hormone and LPS challenges than females within the same cohort (Hulbert et al., 2013; Carroll et al., 2015). Nonetheless, unless male dairy calves are routinely provided colostrum the same diligent as their sisters, the natural sexual dimorphic response to stress and immune challenge will be confounded by this bias toward female calves. Although male calves are raised on a very similar timeline as heifers before weaning (Figure 1), both calf raisers and feedlot managers face the challenge of producing resilient calves that may have FPT.

Transportation During a Critical Window

Calf raisers have limited control over the stress of birth and the short-lived critical window of passive transfer, but many opportunities are available to improve transportation and handling for calves. Almost 1 out of 10 heifers and the majority of dairy-beef calves are transported at 0 to 2 d of age to a specialized calf raising facility (NAHMS, 2007). If this stressor is severe, it may impede immunocompetence. Older animals have developed HPA responses, and a better ability to thermoregulate and control osmolality than newborn calves (Schrama et al., 1992a,b, 1993; Arieli et al., 1995; Gebresenbet et al., 2012). More dehydration and body weight loss in 1-mo-old calves is more noticeable than older calves (Knowles et al., 1997). Among older cattle, transportation causes the release of stress hormones, acute phase proteins, and cytokines (Arthington et al., 2003; Earley and Murray, 2010) and influences innate leukocyte function (Gupta et al., 2007; Burdick et al., 2011; Hulbert et al., 2011b). Buckham Sporer et al. (2007) suggested that transportation stress may reprogram blood neutrophils for a longer lifespan, but also make neutrophils more pro-inflammatory because transportation decreased GC clearance and modulated the expression of neutrophil genes important for the regulation of apoptosis, tissue remodeling, vascular margination (L-selectin), bacterial killing, and wound healing.

Adjustments in the transportation environment, such as ambient temperature, stocking density, distance, and type of road traveled can be adjusted to reduce the stress of transportation (NRC, 2006). Older cattle that rest during transportation display less of a severe stress response than cattle that stand (Knowles et al., 1997; Earley and Murray, 2010; De la Fuente et al., 2012). Calves will likely also benefit from resting during transportation because they retain heat better when they are resting than standing (Schrama et al., 1993). Therefore, the trailer environment and stocking density may contribute to improved recovery rates after transportation (Eicher, 2001; Grigor et al., 2001). Others proposed that analgesics may help alleviate stress because meloxicam reduced the percentage of circulating neutrophils and monocytes in cattle that were transported long distances (Van Engen et al., 2014). These stress-alleviating factors may help older cattle, but transportation-stress abatement methods may be vital for 1-d-old calves that are not fully immunocompetent and do not thermo-regulate like a calf that is over 1 wk old (Liggins, 1994; Gluckman et al., 1999; Bayne, 2003; Teitelbaum and Allan Walker, 2005).

One goal for US calf raisers and researchers should be to determine an appropriate age to transport calves, perhaps using some physiological benchmarks for thermoregulation. In Australia, a best practices standard for transportation is no younger than 5 d of age (Cave et al., 2005; Jongman and Butler, 2013). In Europe, the Federation of Veterinarians used navel healing as an indicator of transport readiness, which means that calves younger than 14 d old are considered unfit to travel (FVE, 2001). Another goal for US calf raisers may be to determine stress-alleviating strategies that are specific to the needs of the vulnerable neonate. If transportation stress is reduced to the same level of stress response caused by gentle handling, then calves potentially may become more resilient to future stressors. For example, mice that were gently handled in the neonatal stage had increased development of HPA programming, as well as increased thyroid and serotonin activity; they became more sensitive to GC feedback (Matthews, 2002).

EARLY-LIFE DISEASE

Adding a stressor like transportation to a young calf may contribute to the rate of enteric disease in the first week of life, when calves are just learning to suckle. Mortality rates are high among US heifers (1 in 10), and over half of these deaths are caused by scours (NAHMS, 2007). Calves are at the greatest risk for enteric disease at age 1 wk, and the risk of respiratory disease steadily increases and plateaus after age 4 wk (Figure 1; Svensson et al., 2003). Most deaths postweaning can be attributed to respiratory disease (NAHMS, 2007).

Calf resilience is a key factor in treating scours. Dehydration and septicemia are the 2 main contributors of mortality and morbidity among scouring calves (Fecteau et al., 1997); therefore, fluid therapies are common treatments. Calves at 1 wk of age that are scouring but remain motivated to stand and suckle are good candidates for oral electrolytes (Smith and Berchtold, 2014). A low-vitality calf is not likely to voluntarily drink oral electrolytes when it is sick during its first

week of life. Low-vitality calves may need either oral drenching or intravenous fluids (Smith and Berchtold, 2014). Calves with underdeveloped gastric systems may not respond to oral electrolytes because the pathogen can make its way into circulation; therefore, veterinarian intervention may be key to increasing survivability from enteric disease.

Another key to improving resilience is early detection of a disease. A prospective study of 795 Holstein calves on 21 commercial dairies indicated that when sickness was detected and treated, calves performed better for their first calving and lactation (Heinrichs and Heinrichs, 2011). Severe early-life infection can permanently alter the central nervous system, affecting feeding behaviors and responsiveness to stress (Karrow, 2006; Hagberg et al., 2012). Young animals that survive a septicemic-like challenge during a critical window have increased GC responses to LPS later in life, but they lack the negative feedback response, so GC stay in the system longer (Spencer et al., 2011). The febrile response and metabolic pathways may also be permanently altered in severely challenged neonatals. Cytokine secretion from macrophages influence the production of cyclooxynegase (COX-2) to convert arachidonic acid into prostaglandin (PGE2), which is the main activator of a febrile response that leads to increased vasoconstriction, reduced heat-abatement strategies (sweating, panting), and increased heat conversion from brown adipose tissue (Spencer et al., 2011). Further investigation for calves is needed to better understand the long-term, epigenetic effects of septicemia and severe dehydration on the regulation of the HPA axis and inflammatory response. Early-life enteric disease among calves may influence calf raisers' ability to detect respiratory disease later in life (Figure 1) because calves may have less of a febrile and behavioral response to respiratory pathogens.

Researchers suggested that the rise in body temperature in a febrile response make the host suboptimal for invading bacteria. (Hart, 1988; Spencer et al., 2011). However, survival is more likely influenced by the increased rate of host defense mechanisms that coincide with a rise in temperature, such as neutrophil migration and phagocytosis (Hart, 1988; Spencer et al., 2011). In addition, fever stimulates the peripheral inflammatory response (or acute phase response), which reduces the amount of iron and zinc available to invading pathogens (Hart, 1988). Activation of the acute phase response is costly due to anorexia and changes in nutrient partitioning; therefore, mature animals with a developed adaptive immunity should have less of a febrile response to immunological challenges (Klasing, 1988; Colditz, 2002).

The severity of dose and onset of acute phase responses following infection make it a challenge to detect sickness in its early stages, especially for respiratory disease in calves (Figure 1; Love et al., 2014). In both respiratory disease and septicemic-like challenge, fever is not always an indicator of the severity of the sickness. The severity of infection did not correspond with fever among 3-wk-old Jersey calves challenged with increased doses of *Escherichia coli* (Ballou et al., 2011). Furthermore, indicators of clinical sickness did not correspond with dose and fever; rather, IL-6 and IFN-γ cytokine secretion and sickness peaked at the same time, just 4 h after the challenge, and the degree of hypoglycemia and circulating zinc related to dose (Maalouf et al., 2010).

Producers commonly observe milk refusals during the pre-weaning to account for sickness (Burton et al., 1992; Elsasser et al., 1997). Decreased feeding during sickness may actually be adaptive for the host (Steiger et al., 1999). For example, mice that were force-fed while infected with *Listeria monocytogenes* were less likely to survive than mice fed ad libitum (Klasing, 1988; Colditz, 2002). In addition, milk replacer nutrition in sick Holstein male calves may have added to the severity of scours and number of calves that required antibiotic treatment (Quigley et al., 1995). Respiratory scoring systems for pre-weaned calves have been evaluated and simplified (Love et al., 2014); however, fecal scoring and enteric disease scoring still need refinement and validation (McGuirk and Collins, 2004; Liang et al., 2016). Calves are highly motivated to drink milk, and may consume milk even at the early stages of sickness; perhaps water and starter intake measures, as well as other nonnutritive oral behaviors may serve as early and better detectors of enteric and respiratory disease. Our laboratories are currently (Hulbert et al., 2015) investigating if automated measures of nonnutritive sucking can be used as an additional measure to detect sickness.

PAINFUL PROCEDURES AND CRITICAL WINDOWS

The AVMA recommends castration and disbudding take place as early in age as possible (Coetzee et al., 2010). A misconception that castration and dehorning is less stressful for young animals likely arose because in older animals have a greater peak of plasma cortisol after castration, and calves lose less weight after castration than older animals (Bretschneider, 2005; Stafforda and Mellorb, 2011). However, as mentioned previously, a high peak of cortisol after a known stressor may be a sign of a well-developed HPA axis (Moberg and Mench, 2000; Mitra et al., 2009). In fact, some scholars argue that pain may be even greater among neonatal animals

compared with mature animals because their nervous system and HPA axis are not developed (Murray and Leslie, 2013). The preferred method for disbudding and castration in the United States are hot-iron cauterization and surgical castration, respectively, but other methods are available (Table 1).

Nonetheless, less tissue is present to excise in young animals undergoing disbudding or castration than in older animals; thus, exposed wounds and risk of infection are less. Webster et al. (2013) provide a general recommendation for both beef and dairy breeds of 3 mo of age, but intact dairy-beef calves are often discounted when dairy-beef calf-raisers sell calves to stockyards and feedlots when they reach around 120 d of age. This is just after calves make it through the commingling stage (Figure 1), when calves are at risk for respiratory disease (NAHMS, 2007). Adding a painful procedure to these other potential stressors is not justifiable to many producers. Therefore, most producers may choose to disbud in the 3- to 4-wk-of-age period (NAHMS, 2007). Castration can be performed surgically or by other methods that induce atrophy of the testes and surround tissues (Fell et al., 1986). Although methods that do not cause an open wound reduce the risk of MAMP exposure, necrotic tissue may still elicit an inflammatory response from DAMP (Figure 2; Hagberg et al., 2012). Surgical castration is the most practiced method for dairy-beef calf raisers (Coetzee et al., 2010). Although castration may reduce aggressive behaviors and modify carcass quality, the primary purpose of castrating cattle for meat consumption is for pregnancy prevention (Price et al., 2003).

Nine out of 10 calf raisers perform castration and disbudding at the same day (Coetzee et al., 2010). Some researchers recommend the procedures be separated from each other, each with an allotted recovery time (Mosher et al., 2013). On the contrary, one may want to limit the number of days the calf spends recovering from these physical stressors and tissue damage. However, when considering the pre-weaned calf timeline (Figure 1), the days in which the calf is not recovering from a stressor or at risk for enteric disease appear to be limited. Ballou et al. (2013) reported that combining surgical castration and iron dehorning has an additive inflammatory effect in the order of sham handling as the least stressful and inflammatory, followed by castration, dehorning, and the combined procedures (handling, castration, and dehorning). The combined procedures caused the greatest secretion of acute phase protein, haptoglobin, and the most inflammatory-driven neutrophils. Thus, a calf with combined procedures may require more recovery days. The 3- to 4-wk age appears to be a logical time to place these procedures because the risk of enteric disease is low, and it is a few weeks before the initiation of weaning. Yet, maternal antibodies in calves without FPT decrease by this age. However, the calf is not without an immune system at this age; its HPA- and immune regulation are still developing, therefore, assistance from analgesic medication is not only logical to reduce pain; they may be providing the calf with some control of the constant innate immune system. For surgical procedures, postoperation use of a nonsteroidal anti-inflammatory drug (e.g., flunixin meglumine) is highly recommended (Huber et al., 2013). It is important to note that flunixin meglumine is the only approved drug for pain relief in calves in the United States (AVMA, 2012).

The additive effect of combining procedures on certain leukocyte measures and haptoglobin (acute phase protein) was attenuated with analgesics (Ballou et al., 2013). Moreover, calves that received analgesics treatment postoperatively returned to performing maintenance behaviors (e.g., grooming, resting, feeding, and drinking) sooner than calves provided no analgesics (Repenning et al., 2013; Sutherland et al., 2013; Webster et al., 2013). Calves that were not provided analgesics displayed more behavioral signs of discomfort than analgesic-treated calves, which included increased head shaking, ear flicking, tail wagging, and foot stamping (Stilwell et al., 2012; Sutherland et al., 2013).

DYNAMIC HOUSING FOR CALVES

Individual housing reduces the risk of disease transmission among hand-fed calves because nose-to-nose contact is limited. Outdoor housing was associated with less disease incidents, but calf-centered improvements in indoor ventilation may change this association (Norton et al., 2010). Whether calves are housed indoors or outdoors, an estimated 7 out of 10 pre-weaned heifers are housed individually in the United States (NAHMS, 2007). In addition to reducing the transmission rate of disease, individual housing facilitates customized care and feeding. Nevertheless, individual housing requires more materials and space than group housing, so many calf housing systems were originally developed to meet the minimum space-allowance requirements for calves (Figure 3). The minimal space allowance requirements that Hurnik and Lewis (1991) prescribed was 60% of the calf's body surface area ($SA = 0.12*BW^{0.60}$); this space allowance formula allows the calf to be able to stand and rest in sternal and lateral recumbency with its legs extended.

The wooden calf hutch met this space requirement for calves that are less than 65 kg (Figure 3). Heifers in the United States in the median percentile weigh 65 kg before wk 5 of age (NAHMS, 2007). As mentioned previously, calf raisers were encouraged set a double birth

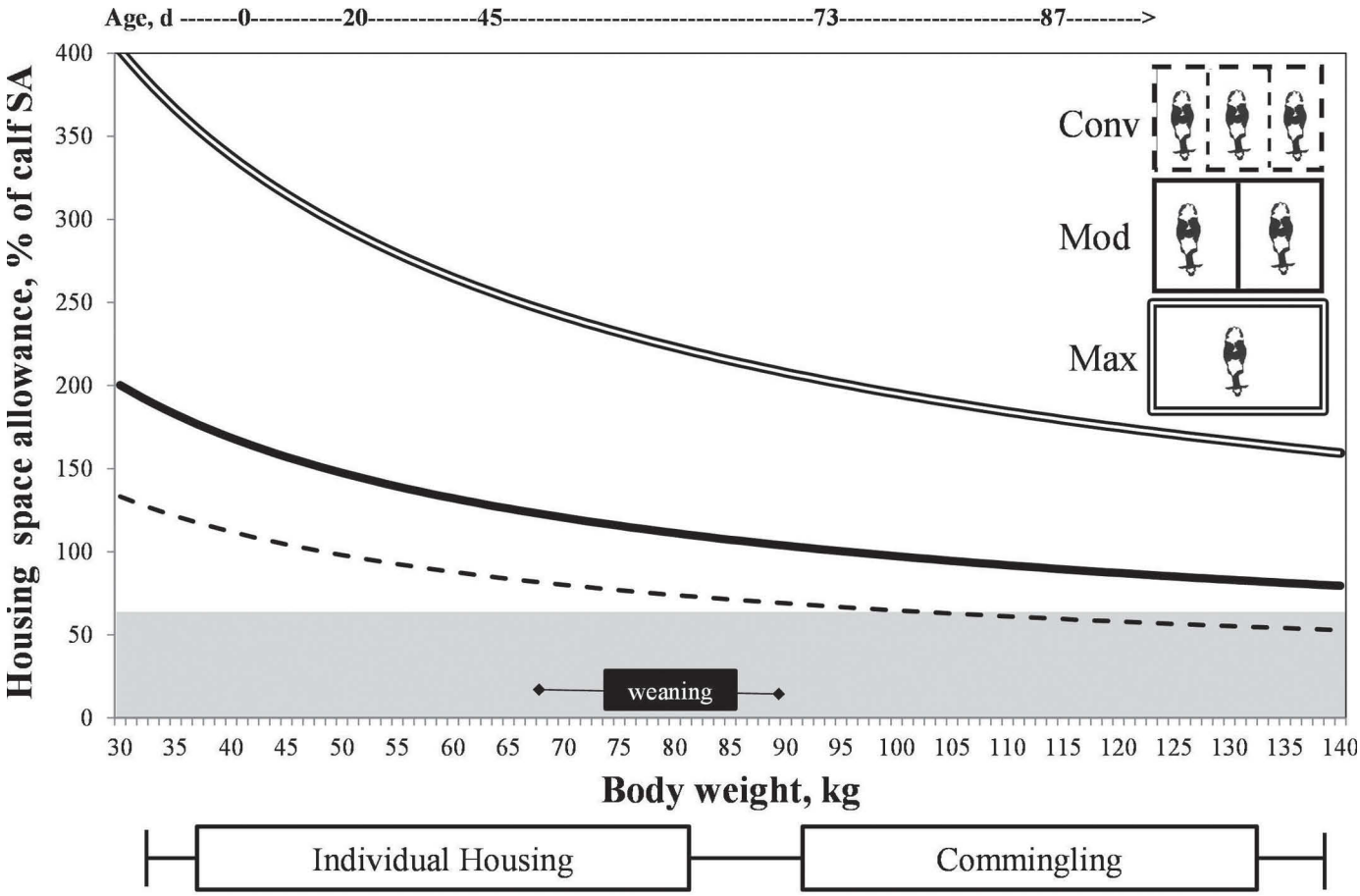

Figure 3. A double-birth weight-by-weaning benchmark influences free space allowance for calves in the conventional wooden hutch system. A recommended benchmark is for the calf to double its birth weight before weaning; on average, heifers double birth weight at 8 wk of age. The absolute minimal space allowance requirements that Hurnik and Lewis (1991) prescribed were 60% (gray region below 60%) of the calf's body surface area (SA = 0.12 × $BW^{0.60}$) for a calf to be able to stand and rest in sternal and lateral recumbency with its legs extended. The conventional wooden hutch (Conv; 1.23 m^2 free space allowance) exceeded this requirement for Holstein bull calves before weaning. However, calves that meet the double-weight benchmark may be subjected to restricted space allowance during and after weaning. Therefore, Conv-hutches (dashed line) were modified to increase space to 1.85 (Mod, solid line) and 3.71 m^2 (Max, double line; Calvo, 2012). Increased BW gain and better regulated immunity were associated with increased BW.

weight by weaning benchmark for calves (Figures 1 and 3) and the current average weaning age is 8.2 wk of age. Some calf raisers are hesitant to place slow-growing calves into group housing after weaning (commingling; Figure 1), and calves can spend up to 90 d of age in hutches designed for 4-wk-old calves (Love et al., 2016). Calvo (2012) demonstrated that modifications can be made to current wooden housing systems to increase space allowance (Figure 3) by 1.5 and 3 times the conventional hutch space. The benefits of increased space allowance for calves were not observed until just before (6 wk) and after weaning (9 wk); calves with greater space allowance had better regulated neutrophils and less basal cortisol secretion after 5 wk of age. In addition, BW and starter consumption was enhanced with increased space allowance. This is just one example of how housing has to be managed as a part of a calf rearing system rather than as separate challenge.

Animals have seasonal immune HPA biorhythms (Walton et al., 2011); therefore, housing and management systems need to be dynamic. Calves are at a greater risk of respiratory disease in the fall season and enteric disease in the summer-fall months (Svensson et al., 2003). The warmer seasons allow for enteric pathogenic bacteria and parasites to thrive (Stilling et al., 2014). In addition, heat stress may play a role by the risk of infection because cattle increase respiratory rate and their circadian activities are disrupted (Collier, 1982). Wooden hutches that are placed on slatted flooring were designed for warm seasons (Love et al., 2016), but plastic hutches were designed only for winter, fall, and spring months (Macaulay et al., 1995).

Calves housed in plastic hutches may require reflective supplemental shade and increased ventilation (Coleman et al., 1996; Carter et al., 2014; Binion and Friend, 2015). A shed system is another dynamic type of housing system that was developed for mild winters and hot summers. Calves housed using this system experienced lower mortality rates, higher health status, and higher hay intakes compared with calves housed conventionally (Murley and Culvahouse, 1957). Portable outdoor individual pens are an aid to keep young calves relatively free from clinical diseases because they can be moved once each week, breaking the life cycle of certain pathogens (i.e., coccidiosis; Davis et al., 1954). The temperature inside plastic hutches can be cooled down by the use of a concrete block placed under the hutch that helps increase ventilation with the subsequent decrease in the levels of carbon dioxide inside the hutch and respiratory rates of the calves (Moore et al., 2012).

However, heat stress abatement methods will not always translate directly into improved feed intake and ADG performance measures for young calves because starter intake is highly variable between calves before weaning (Carter et al., 2014). Water intake is an underutilized behavior observation that could be an indicator of how well the calf is performing under heat stress-conditions when adjusting housing systems for summer months.

During the colder seasons, housing and management systems need to be adjusted with dry bedding so that the calf can insulate itself. Calves can withstand a lower critical temperature when they are provided dry bedding than if they lie down on concrete (Camiloti et al., 2012). Cold stress can cause energy expenditure for thermoregulation and may disrupt resting cycles, especially the REM stage of sleep. In addition, calves tend to display more nutritive and nonnutritive oral behaviors in colder climates (Hanninen et al., 2003; Hepola et al., 2006), and therefore, nutritional strategies need to coincide with housing strategy changes. Calves may benefit during the winter months from paired or group housing because they can rest next to each other to improve thermoregulation (Hanninen et al., 2003; Hepola et al., 2006), but group-housing calves before weaning is not a common practice in the United States (NAHMS, 2007).

Bedding material is also an important factor to consider, especially for winter months (Hill et al., 2011a). In one study, sand was the least sanitary, but long wheat straw had the warmest surface temperature. However, straw bedding had the greatest coliform count after 1 wk of use. In addition, calves were treated more for scours when they were housed on granite fine sand types of bedding than the rice hulls, long wheat, and wood shavings (Panivivat et al., 2004). Furthermore, adequate ventilation efficiently decreased the concentration of air contaminants in closed barn facilities, especially when bedding treatments with acidifiers and antimicrobial products such as sodium bisulfate were applied (Calvo et al., 2010).

Group Housing Calves Before or After Weaning

Calves in the European Union must be group housed by 1 wk of age (Jensen, 2003), but in most US states, producers can choose when to group-house calves. The risk of spreading enteric disease in the first few weeks of life and increased in respiratory disease during first commingling (Figure 1) are the primary factors for delaying group housing (Svensson et al., 2003). In fact, large dairies reported to move individual housed calves to group housing as late as 13 wk of age (NAHMS, 2007).

Cattle are gregarious and are highly motivated to socially interact with each other. Even calves that are individually housed in plastic hutches with pens will mimic each other's behaviors (Miguel-Pacheco et al., 2015). Group-housed calves also are less fearful of novel environments and handling (Table 1; Jensen et al., 1997; Bøe and Færevik, 2003). At commingling, calves may experience increased competition for resources (Jensen and Kyhn, 2000; Krachun et al., 2010), but competition and socially transmitted behaviors may help calves transition from liquid to solid feed at an earlier age (Bach et al., 2010; Cobb et al., 2014b). Transitioning calves into small groups before large groups is highly recommended (Bach et al., 2010; Hulbert and Ballou, 2012). Researchers emphasized the importance of social interactions before first commingling, as increased starter intake and rumen development is associated with pre-weaned group housing (Miguel-Pacheco et al., 2015). For most calves, the motivation to suck on a teat and cross-suck decreases with age, especially as calves transition to high-quality feed and roughage (Jensen, 2003). Some calves never stop cross sucking, and as heifers and cows, some will suck the teats of penmates and steal milk (Jensen, 2003). In male calves, cross and self-sucking can lead to urine ingestion and abomasal hairballs (Terosky et al., 1997). Changes in the design of feeding stations with special stalls and gates to prevent calves from displacing and sucking on each other, or an increase in technology (e.g., radio-frequency identification tag combined with automated feeders) can be used to manage milk feeding stations (Jensen, 2003).

Cross-suckling rates were reduced when calves were provided a dummy nipple during weaning from an automated milk replacer system (Jensen, 2003). In our recent study, conventionally fed calves almost extinguished the use of a dummy nipple at weaning,

but HPN calves tripled their use by 3-fold, which is an indicator that these calves may not have been ready for commingling (Hulbert et al., 2015). Future work will include if dummy nipple use can indicate calf readiness for weaning and prevent cross sucking at commingling.

CONCLUSIONS

Measures of stress resilience and immunocompetence should be added to the definition of performance measures. Traditional performance measures (BW and feed intake) limit the evaluation of the calf raisers' efforts to improve housing and management, especially during the first few weeks of life, when growth rate is highly variable. The investment of labor and resources into these short weeks may be costly, but the long-term benefits may outweigh these initial costs. Further investigation is needed to determine long-term benefits of early-life management strategies. Other than the inevitable stressors of birth and macro-environmental changes, humans possess most of the control and are obligated to help calves become resilient and immunocompetent.

The authors speculate that if enteric disease is not common among calves, then more calf raisers may adopt and develop group-housing and feeding calf systems. If enteric disease is better prevented and managed, then the challenges related to group housing and feeding systems can be better addressed. More labor and technology may be needed to monitor group-housed calves. In addition, transportation of very young calves (<1 wk old) needs further evaluation and reconsideration. Perhaps, calf raisers can provide incentives for dairy producers to improve the management practices during this critical window. A long-term goal for US cattle industries should possibly be to eliminate castration and disbudding altogether, because these procedures, no matter at what age performed, produce an inflammatory response and reduce overall immunocompetence. An open wound, even if small, is a compromised barrier and even closed-wound, sterile tissue damage causes inflammation and HPA activation (Figure 2). Nonetheless, a short-term goal for cattle medicine may include analgesics for calves that experience difficult birth, transportation, and disbudding or castration. The lack of available, approved pain relief and inflammatory control medication is concerning, as this is one of the few ways that cattle producers may be able to justify the use of painful producers to consumers.

Housing and management of hand-fed calves will need to improve and develop as our knowledge increases about immunocompetence and resilience in young animals. With each single change in the hand-fed calf's timeline (Figure 1), several more adjustments will need to follow.

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